Award Number: W81XWH-05-1-0187

TITLE: Molecular Targeting of the P13K/Akt Pathway to Prevent the Development

######Hormone Resistant Prostate Cancer

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REPORT DATE: February 20F€

TYPE OF REPORT: Ø a

PREPARED FOR: U.S. Army Medical Research and Materiel Command

Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;

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6. AUTHOR(S)				5d.	PROJECT NUMBER
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University of Arizona					NUMBER
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12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited					
13. SUPPLEMENTARY	NOTES				
14. ABSTRACT					
					t and progression of prostate
cancer. It is our belief that the PI3K/Akt pathway is the critical pathway that is maintaining survival by blocking apoptosis in the absence of hormonal stimulation. We will use molecular targeting to inhibit the phosphorylation of Akt. Celecoxib is a FDA					
approved COX-2 inhibitor, however unique to celecoxib is its ability to inhibit the phosphorylation of Akt. Celecoxib is a FDA					
off the Pl3k/Akt pathway leading to apoptosis. Celecoxib has been shown to induce apoptosis in a number of different					
					Therefore, in an attempt to improve
					nin et al. synthesized multiple 2nd I thus therapeutic levels can be
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#### Introduction

Our principle hypothesis for the proposal is that combined inhibition of the PI3K/Akt pathway and the androgen pathway will result in a synergistic effect to include: increased apoptosis, decreased proliferation, and a decreased tumor growth.

The rational for our proposal is that hormone refractory prostate cancer has over expression of the PI3K/Akt pathway both at the genomic and protein level implying a significant role in prostate cancer proliferation. Akt has multiple downstream effectors all of which promote growth and survival. There is a direct connection between Akt and the AR that allows Akt to directly activate the AR, and thus activating the androgen pathway. We believe selectively inhibiting both the PI3K/Akt and androgen pathway will cause a synergistic effect. Thus, with combined inhibition, apoptosis will be increased with a corresponding decrease in proliferation ultimately leading to the purpose of our study; a prolongation in patient's survival with metastatic prostate cancer.

### **Body**

<u>Specific Aim 1</u>: Assess the Effectiveness of Combined Hormonal Ablation and PI3K/Akt Pathway Inhibition *In vitro* using a Human Prostate Tissue-Based Organ Culture Model System.

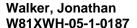
<u>Task</u> 1: Determine the Utility of Using Precision Cut Thin Tissue Sections from Non Radical Prostatectomy Specimens

Currently, we have made no progress in the last 3 years. The conditions here have not been at all conducive to further this project. Difficulties faced over the last 3 years include a persistent lack of support from the Department of Surgery and the College of Medicine. This lack of support was secondary but not limited to a lack of a sitting Department Head or a Dean committed to research or a Section Head, during a majority of this project. Also during this period the section of urology had lost a number of faculty include the head of the section with further responsibility being placed on myself to keep the section and residency program viable. Given these series of events this project has been lingering for the last three years per our multiple discussions. At this time an administrative decision above my level was made to close this project. I had been in discussions with the local VA facility to move the project there however this decision was made prior to my obtaining approval form the parties involved.

<u>Task</u> 2: Determine the Optimal Timing for Evaluation the Effects of a Combined Inhibition.

See above

<u>Task</u> 3: Assessing the Effectiveness of Combined Hormonal Ablation and



PI3K/Akt Pathway Inhibition In vitro using a Thin Tissues Sections

See above.

## **Specific Aim 2 and 3:**

Have not begun at this time see above.

## **Key Research Accomplishments**:

None in the last year.

# **Reportable Outcomes**

We have no reportable outcomes at this time.

#### **Conclusions**

The primary hurdle we had to face is the local academic/financial environment; unfortunately these problems have been identified but never address thus we could restart this project.

**References** – None at this time.

**Appendices** – None at this time.